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10/520,502	01/03/2005	Christopher M Ward	021911.001110US	2720

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EXAMINER

NOBLE, MARCIA STEPHENS

ART UNIT	PAPER NUMBER
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1632

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/520,502	Applicant(s) WARD ET AL.	
	Examiner MARCIA S. NOBLE	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 November 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,4-6 and 8-10 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,4-6 and 8-10 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>9/24/2007</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Claims

1. Claims 1, 2, 4-6, and 8-10 are pending. Claims 1, 4-6, 8, and 9 are amended, and claims 3 and 14 are canceled in Applicant's Response, filed 11/27/2007. Claims 1, 2, 4-6, and 8-10 are under consideration.

Specification

3. The title of the invention was deemed to not be descriptive. Applicant amended the specification to encompass a more descriptive title.

Claim Objections

4. The objection to claim 5 because of the following informalities: Line 2 of claim 5 recited, "primate porcine", which was deemed grammatically incorrect. Applicant amended the claim to correct the recitation. Therefore, the objection is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Upon further consideration of the claims, the instant scope of enablement rejection is being modified to clarify the issues of enablement.

Scope of Enablement

5. Claims 1, 2, 4-6, and 8-10, as amended or previously presented, are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A) A method of detecting mammalian embryonic stem cells undergoing differentiation comprising providing a culture of mammalian ES cells, embryonic carcinoma (EC) cell, or embryonic germ cells (EG) and detecting the cell surface expression of 5T4 antigen in said ES, EC, and EG cells, wherein 5T4 cell surface expression indicates that said ES cell, EC cell, or EG cells are undergoing differentiation.

B) An in vitro method of isolating mammalian embryonic stem cells undergoing differentiation comprising the method of A) and further comprising isolating said cells bound with said antibody, does not reasonably provide enablement for 1) a method of determining differentiation status; and 2) a method of detecting, isolating, or sorting mammalian embryonic stem cells for stem cells undergoing differentiation wherein the absence of 5T4 antigen expression indicates undifferentiated stem cells. Applicant traversed this rejection on following grounds:

1) The instant claims are drawn to a method of detecting the differentiation status of a mammalian ES cell. The breadth of “detecting the differentiation status” encompasses a method that is capable of discerning undifferentiated embryonic stem cells, stem cells that have just entered the process of differentiation, intermediate precursor cells, last stage differentiating cells, and differentiated cells. However, the

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specification only teaches that 5T4 antigen is expressed immediately following the remove of LIF (p. 56, lines 25-30), therefore indicating that 5T4 antigen only corresponds with the early entry of an ES cell into the differentiation process. The specification fails to provide specific guidance to teach that 5T4 antigen would discern undifferentiated ES cells from intermediate precursor cells, or differentiated cells as is encompassed by the breadth of the claims. At the time of the invention, the art only teaches that 5T4 antigen expression is present in trophoblast cells and is upregulated in a variety of carcinoma cells (Boyle et al Hum Gen (1990) 84:455, col 1, par 1, of record in IDS). Therefore the art fails to teach 5T4 antigen as means of discerning the full breadth encompassed by differentiation status as well. Therefore, because the art and the specification fail to support the full breadth encompassed by "detecting the differentiation status", the specification does not enable the full breadth of "detecting the differentiation status" as claimed.

2) The claims encompass a method of detecting, isolating, or sorting mammalian ES cells, wherein the absence of 5T4 antigen expression indicates undifferentiated stem cells (see claim 2) or cell not bound by 5T4 antigen antibody sort undifferentiated stem cells from stem cells undergoing differentiation.

To clarify this aspect of the enablement rejection, Applicant is referred to the art of Boyle et al. (1990). Boyle et al teaches that 5T4 antigen is expressed on the cell surface of trophoblast cells and amniotic epithelium. This is consistent with the teachings of the specification which disclosed that 5T4 antigen was originally isolated from human placental trophoblast cells (p. 3, lines 1-2). Boyle et al further teaches that

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the 5T4 antigen expression is limited to a few epithelial cells (p. 455, col 1, par 1).

Since the art suggests that the 5T4 antigen is restricted to only a few differentiated cell types, the art is demonstrating that many adult differentiated epithelial cells and differentiated non-epithelial cells do not express 5T4 antigen. Therefore, the art implies that the absence of 5T4 antigen expression does not necessarily indicate that a stem cell is an undifferentiated stem cell because the absence of 5T4 antigen would not discern between an undifferentiated ES cell and a differentiated cell that does not express 5T4 antigen, as taught by Boyle et al. Therefore, because the art and the specification indicate that 5T4 antigen expression is not expressed in some differentiated cell types, a method that detects, isolates, or sorts out undifferentiated stem cells by the absence of 5T4 antigen expression or absence of binding to a 5T4 antigen antibody would not predictable identify or isolate undifferentiated stem cells as is encompassed by the claims. Therefore, the specification does not enable a method of detecting, isolating, or sorting out undifferentiated ES cells by the absence of 5T4 antigen or lack of binding to a 5T4 antigen antibody.

Applicant traverses this rejection as originally stated in the Non-Final Office action, mailed 7/27/2007. Applicant states the absence of differentiation markers, NF-68, and fgf-5, only indicates that the stem cell is not of that specific germ-layer lineage and does not necessarily indicate that the stem cell is not undergoing differentiation or is not a differentiated cell" (see page 6 of remarks, filed 11/27/2007). Applicant further points to Fig 12a and figures 24-27 to demonstrate that known undifferentiated ES cells expressing OCt-4 are not expressing 5T4 antigen in the presence of LIF but then begin

to express 5T4 antigen when LIF is removed (pages 6 and 7 of remarks, filed 11/27/2007).

Applicant's arguments are not found persuasive. However, because the use of Ward et al in the enablement rejection of the Office Action, mailed 7/27/2007, may not have clearly demonstrated that the absence of 5T4 antigen does not necessarily indicate an undifferentiated ES cell, the rejection was reiterated above using the art of Boyle et al to clarify the rejection.

3) In the previous Office Action, mailed 7/27/2007, the breadth of the claims encompassed embryonic and adult stem cell. However, adult stem cells were deemed to lack enablement. (see par bridging pp. 6 and 7 and last par on p. 7). Applicant asserts that the claims have been amended to recite mammalian embryonic stem cell because Examiner indicated this as enabled subject matter. Applicant's argument is found persuasive. The amendment to the claims obviates this aspect of the enablement rejection. Therefore, this aspect of the enablement rejection is withdrawn.

4) The instant invention was deemed to lack enablement for detection and isolation of cells by using any means to detect 5T4 antigen. Applicant traverses this argument on the ground that the specification teaches multiple means of detecting 5T4 antigen including mRNA analysis (page 7 or remarks, filed 11/27/2007). This argument is not found persuasive because as previously indicated in the Office Action, mailed 7/27/2007, Ward et al teaches that 5T4 antigen was expressed in some embryonic stem cell populations that were and were not undergoing differentiation and that the

expression of 5T4 antigen on the cell surface need to be the critical indicator rather than transcripts (par bridging pages 10 and 11).

Applicant also asserts that the claims have been amended to recite "detecting cell surface expression of 5T4 antigen". Because the art indicates that cell surface expression of the 5T4 antigen protein is the critical indicator of differentiation status, Applicants argument is found persuasive and this ground of rejection is address by the amendment to the claims.

5) The instant invention was deemed to lack enablement for "differentiated stem cells". Applicant traverses this rejection on the grounds that the claims now encompass "undergoing differentiation" and this obviates the ground of enablement. Applicant's argument is found persuasive, and therefore, this issue of enablement is addressed by the amendments to the claims.

Because Applicant's amendment to the claims and arguments were unable to address and obviate all the issues of enablement of record, the instant scope of enablement rejection is maintained.

Therefore, in summary, the amendment to the claims and Applicant's arguments were not able to obviate all aspects of the enablement rejection of record. The specification and art still fail to support the full breadth of a method of detecting the differentiation status of a mammalian ES cell as claimed using 5T4 antigen, because 5T4 antigen only identifies cells in the early stages of differentiation. The specification also does not support a method that uses the absence of 5T4 antigen as an indicator of undifferentiated ES cell because the art teaches that the absence of 5T4 antigen would

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not discern between an undifferentiated cell and the many differentiated cells types that do not express 5T4 antigen as taught by Boyle et al. Therefore, the absence of 5T4 antigen expression or the lack of binding to a 5T4 antigen would not predictably identify, isolate, or sort out an undifferentiated ES cell as claimed. Because the above issues of enablement remain, the enablement rejection as previously and presently set forth is maintained.

112, 2nd Paragraph Rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. The rejection of claims 2-6, 8-10, and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 8, 9, and 14 recited, "differentiated stem cells". Applicant removed this recitation by amendment. Therefore, this rejection is withdrawn.

Claim 9 recites the limitation "the cells", which lacked antecedent basis. Applicant amended the claims to recite "the bound or unbound cells", which clarifies the claim. Therefore, the rejection is withdrawn.

Claim 14 was rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the

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steps. See MPEP § 2172.01. Claim 14 has been canceled. Therefore this rejection is withdrawn.

7. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Marcia S. Noble

/Peter Paras, Jr./
Peter Paras, Jr.
Supervisory Patent Examiner, Art Unit 1632